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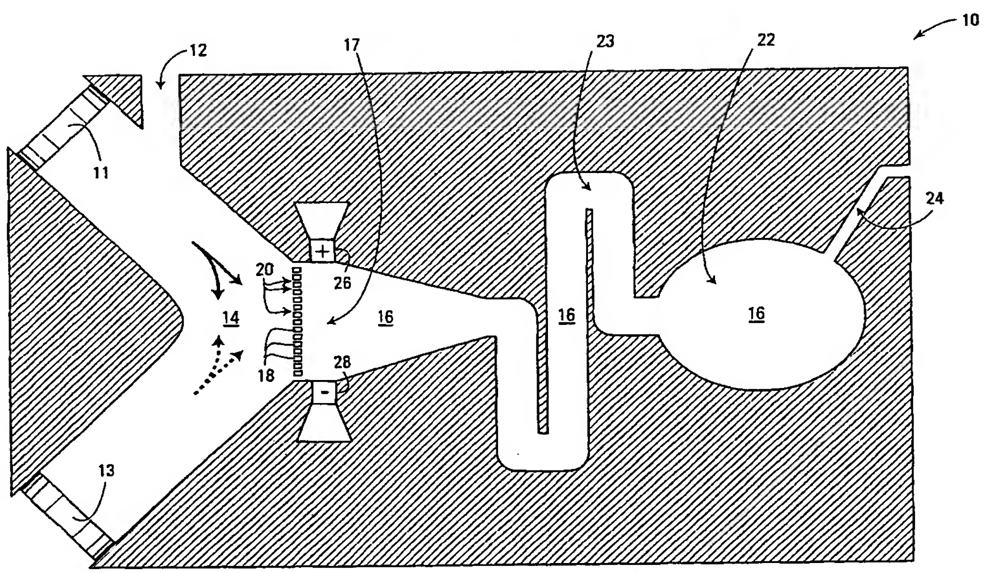

(57) **Abstract:** The invention relates to methods and devices for detecting the presence of a particle of interest (hereinafter an analyte particle) in a fluid. A detection device exemplary of the present invention filters a sample of the fluid to remove particles larger than the analyte particles. A reagent solution, containing reagent particles smaller than the analyte particles, is then added to the sample. The reagent particles will react with the analyte particles, if any are present, to form reagent-analyte complexes which are larger than the analyte particles. The sample is then filtered a second time to remove particles the same size as or smaller than the analyte particles. The sample is then tested for the presence of reagent-analyte complexes to detect the presence of the analyte particle in the fluid.

WO 2004/113919 A2

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NANO AND MICRO-TECHNOLOGY VIRUS DETECTION METHOD AND DEVICE

FIELD OF THE INVENTION

[0001] The present invention relates to methods and devices for detecting the presence of analyte particles, such as viruses, in a biological fluid.

BACKGROUND OF THE INVENTION

[0002] Controlling the spread of infectious diseases is a significant challenge facing society today. In meeting this challenge, effective and efficient methods of virus detection are critical.

[0003] While many techniques of virus detection are known and in use, they have several disadvantages. For example, many detection tests must be performed by skilled technicians in laboratories. This increases both the cost of the test and the time it takes to obtain results. Additionally, many detection tests are performed on blood samples, and so typically the blood sample must first be taken by a skilled technician in a laboratory, clinic or hospital setting. Again, this causes the tests to be more expensive and time consuming, as well as, possibly inconvenient for the person being tested.

[0004] The necessary involvement of skilled technicians also makes most current tests inappropriate for home testing. For people who have difficulty leaving their homes or who live in remote areas, such tests are inconvenient. Such tests are also undesirable for people who are reluctant to have others know they are being tested for a particular virus. In some cases, a person may be stigmatized for simply being a suspected carrier of a virus. Many people would prefer at-home testing to avoid this possibility.

[0005] Another disadvantage of some known detection devices, is that they must be discarded after a single use. Often, because potentially hazardous

biological fluids are involved, special precautions must be taken in their disposal. Again, this may add to the expense of such devices while making them less convenient.

[0006] Furthermore, many known tests do not detect the virus itself, instead they detect the antibodies that an infected person's body produces in response to the virus. As a result, there is often a delay after a person becomes infected with a virus before its presence can be detected. For standard human immunodeficiency virus (HIV) tests, which rely on antibody detection, it can take anywhere from three months to a year from the date of infection for a body to produce enough anti-HIV antibodies to test positive.

[0007] Accordingly, there is need for an inexpensive, fast and convenient method and device for virus detection.

SUMMARY OF THE INVENTION

[0008] The invention relates to methods and devices for detecting the presence of a particle of interest (hereinafter an analyte particle) in a fluid. A detection device exemplary of the present invention filters a sample of the fluid to remove particles larger than the analyte particles. A reagent solution, containing reagent particles smaller than the analyte particles, is then added to the sample. The reagent particles will react with the analyte particles, if any are present, to form reagent-analyte complexes which are larger than the analyte particles. The sample is then filtered a second time to remove particles the same size as or smaller than the analyte particles. The sample is then tested for the presence of reagent-analyte complexes to detect the presence of the analyte particle in the fluid.

[0009] Detection devices exemplary of the present invention can be fabricated using nanotechnology and microtechnolgy techniques. Preferably, devices exemplary of the present invention are hand-held devices suitable for

home use. They may be mechanically controlled by a user or electronically controlled by a processing element. Advantageously, devices exemplary of the present invention can be either disposable or reusable.

[0010] In accordance with an aspect of the present invention , a method for detecting the presence of an analyte particle in a fluid, the method including, sequentially: filtering a sample of the fluid to remove particles in the sample larger than the analyte particle; adding to the sample a reagent that interacts with the analyte particle to form an analyte particle-reagent complex that is larger than the analyte particle; filtering the sample to remove particles from the sample that are smaller than the analyte particle-reagent complex; testing the sample for the presence of the analyte particle-reagent complex to detect the presence of the analyte particle in the fluid.

[0011] In accordance with a further aspect of the present invention, a lab-on-a-chip for detecting the presence of an analyte particle in a fluid, including: a first chamber for receiving a sample of the fluid; a second chamber for receiving a reagent that reacts with the analyte particle in the sample to form an analyte particle-reagent complex, larger than the analyte particle; a filter in flow communication with the second chamber, the filter sized to pass the analyte particle, and block the analyte particle-reagent complex; and a detector for detecting the presence of the analyte particle-reagent complex in the second chamber.

[0012] Other aspects and features of the present invention will become apparent to those of ordinary skill in the art upon review of the following description of specific embodiments of the invention in conjunction with the accompanying figures.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] In the figures which illustrate by way of example only,

embodiments of this invention:

[0014] **FIG. 1** is a cross-sectional top view of a virus detection device, exemplary of an embodiment of the present invention;

[0015] **FIG. 2** is an enlarged schematic view of a portion of the device of **FIG. 1** showing the flow of a blood sample;

[0016] **FIG. 3** illustrates a virus and protein particles reacting to form a virus-protein complex;

[0017] **FIG. 4** is another enlarged schematic view of a portion of the device of **FIG. 1** showing the flow of the blood sample through in the direction opposite that of the flow shown in **FIG. 2**; and

[0018] **FIG. 5** is a cross-sectional top view of a virus detection device, exemplary of another embodiment of the present invention.

DETAILED DESCRIPTION

[0019] **FIG. 1** illustrates a virus detection device **10**, exemplary of an embodiment of the present invention. Preferably, the device is a hand-held device known as a "lab-on-a-chip", manufactured using microtechnology or nanotechnology fabrication methods.

[0020] Nanotechnology and microtechnology fabrication methods are generally known in the art. Nanotechnology permits the creation, use, or manipulation of objects at the nanoscale, usually in the 0.01 to 100 nanometer (nm) range. Microtechnology operates similarly at the larger microscale. Nanotechnology and microtechnology manufacturing processes, materials, and devices are used in a wide variety of fields including microelectromechanical systems (known as MEMS), nanomaterials, and microfluidic systems. As micro and nanoscale research advances, it is expected that the sophistication with which such devices can manipulate objects on the nanoscale will grow while the cost of these devices will decrease.

[0021] Nanotechnology and microtechnology techniques allow fabrication of "Lab-on-a-chip" devices. "Lab-on-a-chip" devices analyze tiny drops of fluids or chemicals in short periods of time using microfluidic channels. These devices integrate mixing, incubation, separation, detection and data processing in a hand-held device. Such devices may, for example, be fabricated from micro-injection molded plastic. Alternatively, they may be fabricated using LIGA process or any other method known in the art. Embodiments of the present invention exploit "lab-on-a-chip" technology to provide a portable device for virus detection.

[0022] In the following description virus detection device **10** is discussed in the context of detecting HIV in a blood sample, however, the device is not so limited. For example, device **10** could be used with biological fluids other than blood, for example, saliva, urine, or embryonic fluid. It could also be used to assay non-biological fluids such as waste water, drinking water, or any other liquid medium containing analyte particles of interest. Analyte particles other than viruses could also be detected, for example, proteins or bacteria.

[0023] Device **10** is preferably a hand-held device. The micro-formed components have dimensions on the order of micrometers, as will be described in greater detail below, while the overall dimensions will vary depending on the size of the housing.

[0024] Device **10** includes an opening **12** for receiving a biological fluid, such as blood; a first fluid chamber **14**; and a second fluid chamber **16**. Device **10** may also include a one-way exit valve (not shown) to enable air and other gases to escape from the device. Opening **12** leads to first fluid chamber **14**. While opening **12** is depicted in **FIG. 1** as leading from the side of device **10**, alternatively it may lead from the top of device **10** so that the biological fluid would be induced to flow into first fluid chamber **14** by gravity. Opening **12** may also include a one-way valve to prevent fluid backwash.

[0025] First fluid chamber **14** is preferably generally V-shaped as shown in **FIG. 1**. Preferably, the arms of the 'V' may have a square cross-section with a width between 20 micrometers and 1 millimeter. They may be several millimeters in length.

[0026] Pushing elements **11** and **13** are located at the end of each arm of first fluid chamber **14**. Pushing elements **11** and **13** may take the form of plungers, formed as flexible diaphragms. Alternatively, pushing elements **11** and **13** could be pistons or piezoelectric elements.

[0027] At the apex of the 'V', separating first fluid chamber **14** from second fluid chamber **16**, is a filter **18**, having a plurality of apertures **20**. Filter **18** may have between 5 and 100 apertures **20**. Apertures **20** extend the full height of second fluid chamber **16** and are preferably wide enough so as to allow the analyte particles of interest, if any are present, to pass but to block any particles larger than the analyte particles. For example, for a device **10** to detect HIV, apertures **20** can have a width of between 80 and 150 nm. Various other configurations of apertures will be obvious to a person skilled in the art.

[0028] Second fluid chamber **16** has an approximate height of 1100 nm and includes a detection area **17**; a mixing channel **23**; and a collecting chamber **22**. In contact with the interior space of detection area **17** of second fluid chamber **16** are two electrodes **26** and **28**. Detection area **17** is in fluid communication with collecting chamber **22** by way of mixing channel **23**. Mixing channel **23** is a generally serpentine passageway, approximately 550 nm in width. For simplicity, mixing channel **23** is shown in **FIG. 1** with two turns, although it may include more. Collecting chamber **22** is preferably generally circular shaped in order to facilitate mixing of fluids within it. A passageway **24** leads to collecting chamber **22** and enables a reagent solution to be introduced to collecting chamber **22**. The reagent solution may initially be contained in a reagent chamber (not shown) in fluid communication with passageway **24**. For example, the reagent chamber could be a disposable cartridge. Alternatively, the

reagent solution may be added by way of a syringe or otherwise. As with opening **12**, passageway **24** is depicted in **FIG. 1** as leading from a side of device **10**, however, it could alternatively lead from the top of device **10**. It may also include a one-way valve to prevent fluid backwash.

[0029] The operation of device **10** can be best described with reference to **FIGS. 1-4**. A blood sample **30** is introduced to first fluid chamber **14** through opening **12**. Blood sample **30** can be of the order of ten microliters in volume and can therefore be provided from a small prick in the finger of a person being tested. Blood sample **30** includes red blood cells **32**, white blood cells (not shown) and, other smaller particles **34** such as water, proteins, minerals, and the like. Blood sample **30** may also include analyte particles, the presence of which is to be detected. In the embodiment shown in **FIGS. 2-4** the analyte particle to be detected is HIV **36**. Optionally, an anti-clotting agent may also be added to first fluid chamber **14** to prevent clotting in blood sample **30**.

[0030] Once introduced to first fluid chamber **14**, blood sample **30** is urged to flow in the directions indicated by the solid-line arrows shown in **FIG. 1** by the inward stroke of pushing element **11**. Pushing elements **11** and **13** may be moved back and forth in a coordinated fashion, so that the inward stroke of pushing element **11** coincides with the outward stroke of pushing element **13**. In this way, the direction of the flow of blood sample **30** in chamber **14** is reversed to flow in the directions indicated by the broken-line arrows shown in **FIG. 1** on the inward stroke of pushing element **13**. Preferably, the flow of sample **30** in first fluid chamber **14** will be reversed several times. In this way, blood sample **30** flows along the surface of filter **18** repeatedly with a portion of sample **30** flowing transversely and through filter **18** each time.

[0031] The flow of sample **30** from first fluid chamber **14** to second fluid chamber **16** may best be described with reference to **FIG. 2**. Again, apertures **20** of filter **18** are preferably sized so that they allow HIV **36** and smaller particles **34** to pass through filter **18** to second fluid chamber **16** but block the passage of

particles larger than HIV **36** such as red blood cells **32** and white blood cells (not shown). By repeatedly reversing the direction of the flow of sample **30** in first fluid chamber **14**, the larger particles are discouraged from blocking or clogging apertures **20**.

[0032] Blood sample **30**, including HIV **36**, if present, and smaller particles **34**, thus flows through filter **18** to second fluid chamber **16**. In second fluid chamber **16**, blood sample **30** flows from detection area **17**, through mixing channel **23** into collecting chamber **22**. Once blood sample **30** reaches collecting chamber **22**, a reagent solution is added to it. The reagent solution is preferably introduced through passageway **24**. The reagent solution contains reagent particles that will react with analyte particles, if any are present, to form reagent-analyte complexes. The reagent particles are smaller in size than the analyte particles, the presence of which is to be detected. For example, the reagent solution can contain truncated CD4 glycoprotein particles **38**. CD4 glycoprotein is commonly found in the human body on the surface of white blood cells known as T lymphocytes, or T cells. On the surface of a T cell, CD4 provides a binding site for HIV thus enabling HIV to infect the T cell. A soluble, truncated form of CD4 **38**, not associated with T cells, will bind with HIV **36** to form a CD4-HIV complex **40**. This is depicted in **FIG. 3**. CD4-HIV complex **40** is larger than both CD4 **38** and HIV **36** individually.

[0033] Preferably, a suitable amount of 50% (wt/v) CD4 solution is added. For example, enough CD4 may be added to create about a **1** to **1** ratio by volume between the CD4 solution and the pre-filtered blood sample **30**. Assuming HIV **36** is present in blood sample **30**, some of the HIV **36** and some of the CD4 **38** present in collecting chamber **22** will react to form CD4-HIV complexes **40**. Mixing, and thus reacting, of HIV **36** and CD4 **38** is further encouraged by inducing sample **30**, including the CD4 **38** that has been added to it, to flow from collecting chamber **22**, through mixing channel **23** to detection area **17**, i.e. from right to left in second fluid chamber **16** as depicted in **FIG 1**. This flow may be induced by the fluid pressure of the reagent solution entering

collecting chamber **22** through passageway **24** or otherwise.

[0034] As sample **30** flows through mixing channel **23**, more HIV-CD4 reactions occur and the concentration of CD4-HIV complexes **40** rises. As depicted in **FIG. 4**, when the mixture reaches filter **18**, the force of the flow will cause smaller particles **34** and any unreacted CD4 **38** and HIV **36** to pass through filter **18** to first fluid chamber **14**. As described above, the size of apertures **20** is chosen so as to allow HIV **36** to pass through filter **18** but to block any particles larger than HIV **36**. Therefore, because CD4-HIV complexes **40** are larger than simple HIV **36** they will not pass through filter **18** and thus remain in second fluid chamber **16**.

[0035] Preferably, and to ensure that substantially all unreacted CD4 **38** and HIV **36** passes through filter **18** into first fluid chamber **14**, after the CD4 solution has been introduced through passageway **24**, distilled water may be forced through passageway **24** or introduced into collecting chamber **22** by any other method, so that it will flow through device **10** towards first fluid chamber **14**.

[0036] The presence of CD4-HIV complexes **40** in second fluid chamber **16** can now be detected by a sensing circuit. The sensing circuit includes electrodes **26** and **28**, which are in contact with the interior space of detection area **17** of second fluid chamber **16** and a voltage source (not shown), and a suitable conventional electronic circuit capable of detecting and communicating a change in resistivity. CD4-HIV complexes **40** in detection area **17** will affect the resistivity between electrodes **26** and **28**. For example, in the absence of other fluids in detection area **17**, a low resistivity indicates the presence of CD4-HIV complexes **40**, while a high resistivity indicates their absence. The sensing circuit can thus determine this resistivity to detect their presence. A positive test result can be communicated to the user.

[0037] If no HIV **36** is present in blood sample **30**, no CD4-HIV reactions will occur and no CD4-HIV complexes **40** will be formed. Therefore, the sensing circuit will detect a higher resistivity between electrodes **26** and **28** and a

negative test result can be communicated to the user.

[0038] Conveniently, device **10** may be disposable. It would thus be suitable for personal home use. Optionally, however, device **10** could be made to be reusable. For example, a cleaning solution, such as 30% (v/v) hydrogen peroxide, could be introduced to device **10** to disinfect its chambers and passageways between uses.

[0039] . Device **10** may be operated by a user mechanically moving pushing elements **11** and **13** and activating valves (not shown) to release reagent solution, and possibly other fluids, into chambers **14** and **16**. Alternatively, the pushing elements and valves of device **10** may be electronically controlled by a processing element (not shown). In this embodiment, pushing elements **11** and **13** could be electronic or electro-mechanical, formed for example as piezoelectric diaphragms. Conveniently, the processing element may also be used with the sensing circuit to detect the presence of the virus.

[0040] A person of ordinary skill will now appreciate that the present invention could easily be embodied in a variety of configurations. For example, **FIG. 5** depicts another possible embodiment of a virus detection device exemplary of the present invention **10'**. Device **10'** includes two separate filters **18'** and **18"**. For ease of reference, the elements of **FIG. 5** are labeled with the same numbers as their corresponding functional counterparts in **FIG. 1** but with the prime (') or double-prime (") symbol. Device **10'** may also be formed in plastic by micro-injection molding methods or by any other method known in the art. In device **10'** the flow of blood sample **30** is unidirectional, i.e. from left to right in **FIG. 5**.

[0041] Device **10'** includes: a first fluid chamber (not shown); a first filter **18'** having apertures **20'**; a second fluid chamber **16'** which includes a serpentine mixing channel **23'** and a detection chamber **17'** which is generally round in shape; a passageway **24'** through which reagent solution is introduced; electrodes **26'** and **28'** which are in contact with the interior of detection chamber

17'; and a second filter **18"** having apertures **20"**.

[0042] In operation, after blood sample **30** is introduced to a first fluid chamber (not shown) of device **10'**, it is urged to flow through first filter **18'**. First filter **18'** has apertures **20'** which, like apertures **20** of device **10**, are sized to allow analyte particles, HIV **36** in the present example, and smaller particles **34** to pass through but to block any particles larger than the analyte particles. After passing through first filter **18'**, sample **30** is then induced to flow through mixing chamber **23'** of second fluid chamber **16'**. At a point near the entrance of mixing channel **23'** as depicted in **FIG. 5**, reagent solution containing CD4 particles **38** is added to sample **30** through passageway **24'**. Sample **30**, including CD4 particles **38**, continues to flow through mixing channel **23'**. Assuming HIV **36** is present in sample **30**, some of the HIV **36** and CD4 **38** will react to form CD4-HIV complexes **40**..

[0043] When sample **30** reaches detection chamber **17'** of second fluid chamber **16'** and second filter **18"**, the force of the flow will cause smaller particles **34** and any unreacted CD4 **38** and HIV **36** to pass through second filter **18"**. Again, the size of apertures **20"** is chosen so as to allow HIV **36** to pass through filter **18"** but to block any particles larger than HIV **36**. Therefore, because CD4-HIV complexes **40** are larger than simple HIV **36** they will not pass through second filter **18"** and thus remain in detection chamber **17'** of second fluid chamber **16'**.

[0044] The presence of CD4-HIV complexes **40** in detection chamber **17'** can now be detected by a sensing circuit that includes electrodes **26'** and **28'** in a manner similar to that described for device **10**. Indication of a positive test result can be communicated to the user. If no HIV **36** is present in sample **30**, the absence of any CD4-HIV complexes **40** in detection chamber **17'** will be detected and a negative test result will be communicated to the user.

[0045] Of course, the above described embodiments are intended to be illustrative only and in no way limiting. The described embodiments of

carrying out the invention are susceptible to many modifications of form, arrangement of parts, details and order of operation. The invention, rather, is intended to encompass all such modification within its scope, as defined by the claims.

WHAT IS CLAIMED IS:

1. A method for detecting the presence of an analyte particle in a fluid, said method comprising, sequentially:

   filtering a sample of said fluid to remove particles in said sample larger than said analyte particle;

   adding to said sample a reagent that interacts with said analyte particle to form a reagent-analyte particle complex that is larger than said analyte particle;

   filtering said sample to remove particles from said sample that are smaller than said reagent-analyte particle complex;

   testing said sample for the presence of said reagent-analyte particle complex to detect the presence of said analyte particle in said fluid.

2. A method in accordance with claim 1, wherein said fluid is a biological fluid.

3. A method in accordance with claim 2, wherein said biological fluid is blood.

4. A method in accordance with claim 3, wherein said analyte particle is human immunodeficiency virus.

5. A method in accordance with claim 1, wherein said analyte particle is a virus.

6. A method in accordance with claim 4, wherein said virus is human immunodeficiency virus.

7. A method in accordance with claim 6, wherein said reagent is truncated CD4 glycoprotein.

8. The method of claim 7, wherein said filtering is performed using micro-injected molded plastic.

9. A lab-on-a-chip for detecting the presence of an analyte particle in a fluid, comprising

   a first chamber for receiving a sample of said fluid;

   a second chamber for receiving a reagent that reacts with said analyte particle in said sample to form a reagent-analyte particle complex, larger than said analyte particle;

   a filter in flow communication with said second chamber, said filter sized to pass said analyte particle, and block said reagent-analyte particle complex;

   a detector for detecting the presence of said reagent-analyte particle complex in said second chamber.

10. The lab-on-a-chip of claim 9, wherein said filter is in flow communication with said first chamber, to block particles larger than said analyte particle from passing from said first chamber to said second chamber.

11. The lab-on-a-chip of claim 9, further comprising a second filter in flow communication with said first chamber and said second chamber, to block particles larger than said analyte particle from passing from said first chamber to said second chamber.

12. The lab-on-a-chip of claim 9, wherein said fluid is a biological fluid.

13. The lab-on-a-chip of claim 12, wherein said biological fluid is blood.

14. The lab-on-a-chip of claim 9, wherein said analyte particle is a virus.

15. The lab-on-a-chip of claim 14, wherein said virus is human immunodeficiency virus.

16. The lab-on-a-chip of claim 15, wherein said reagent is truncated CD4 glycoprotein.

17. The lab-on-a-chip of claim 9, wherein said second chamber comprises a serpentine mixing passage for mixing said reagent with said analyte particle in said sample.

18. The lab-on-a-chip of claim 9, wherein said detector comprises an electrode for electrically detecting presence of said reagent-analyte particle complex in said second chamber.

19. The lab-on-a-chip of claim 15, wherein said filter is sized to block particles larger than 110 nanometers.

20. The lab-on-a-chip of claim 9, further comprising a pushing element for urging said sample through said filter.

21. The lab-on-a-chip of claim 20, wherein said pushing element is electronically controlled, and further comprising a processor to control said pushing element.

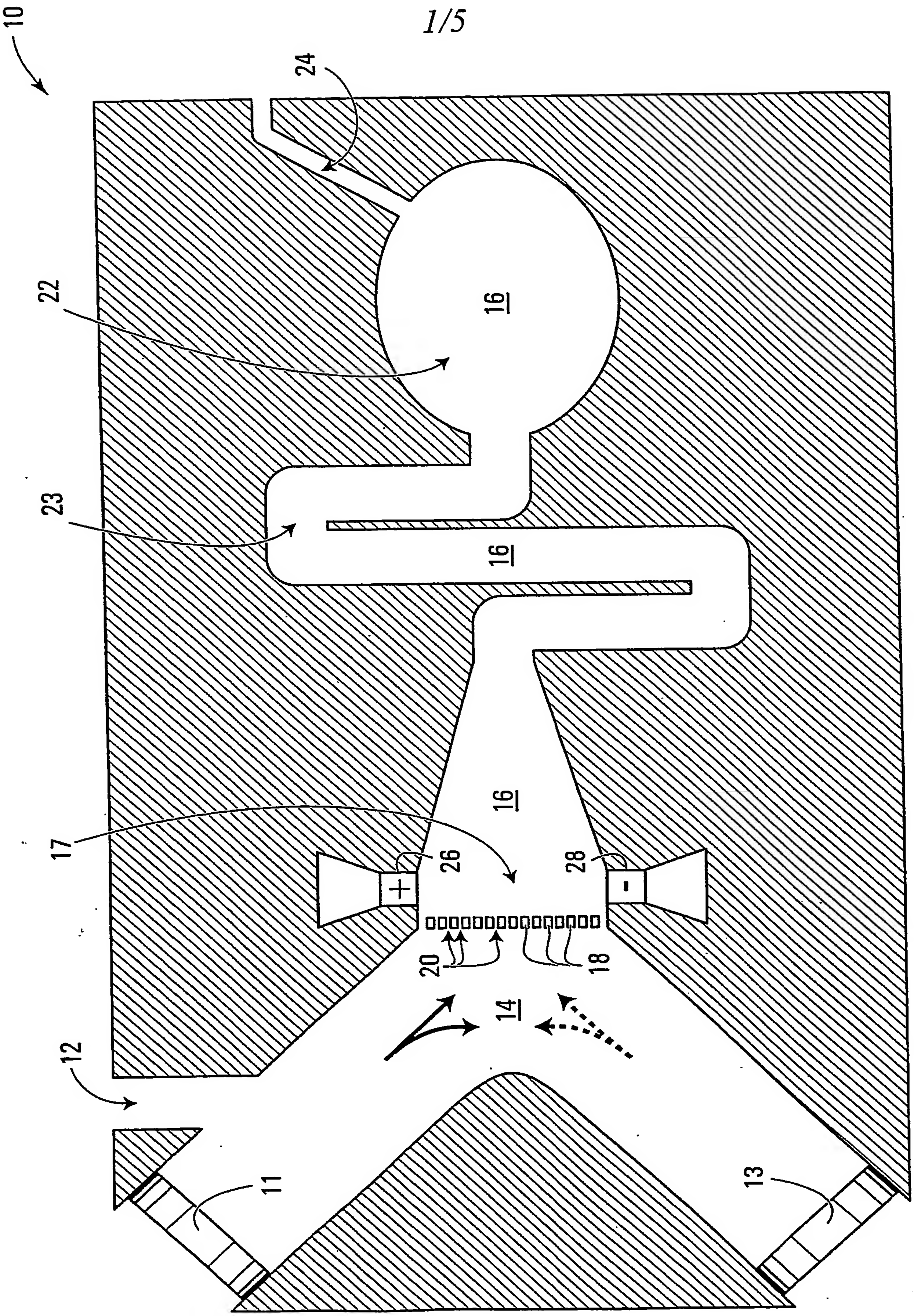
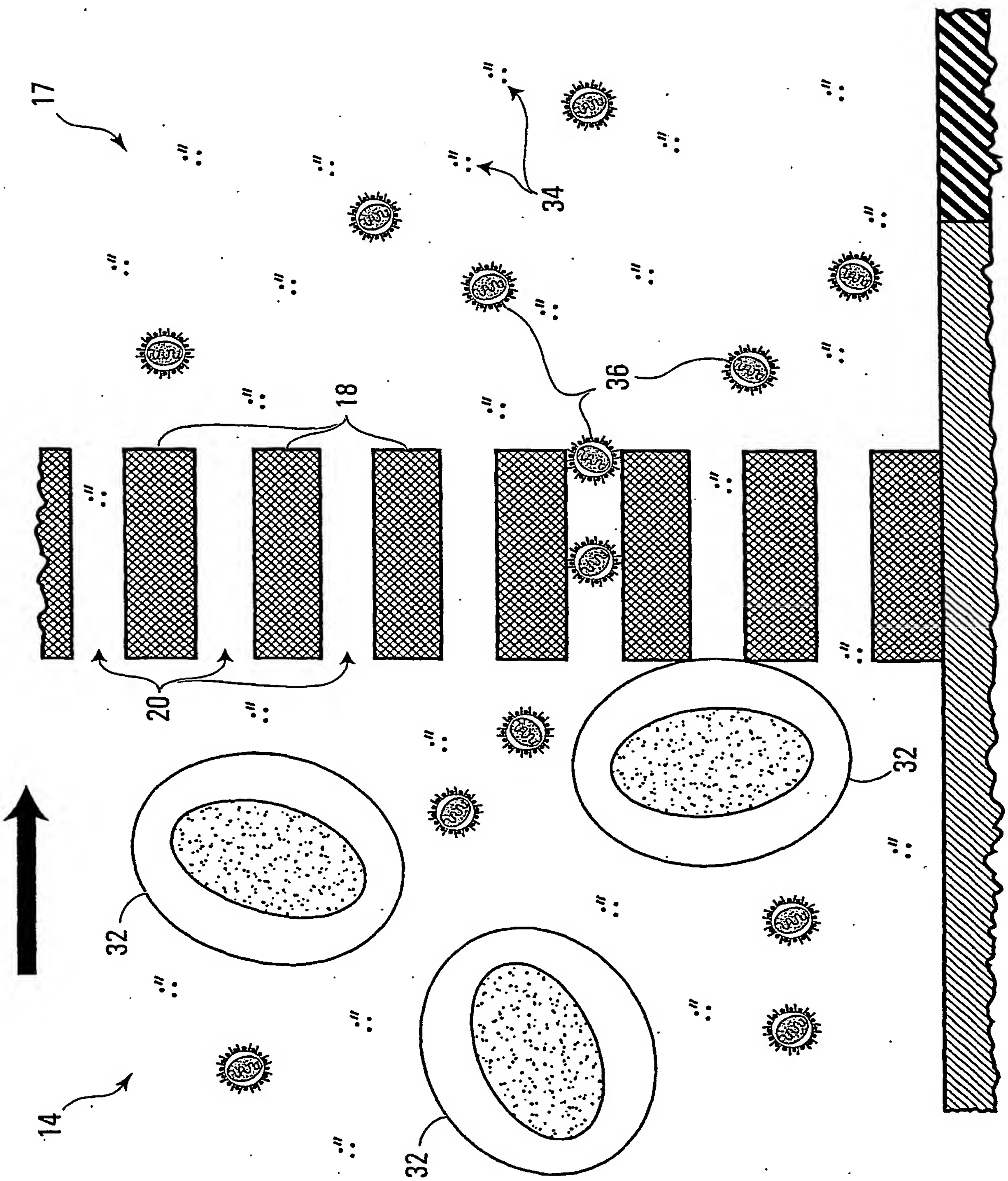


FIG. 1

FIG. 2



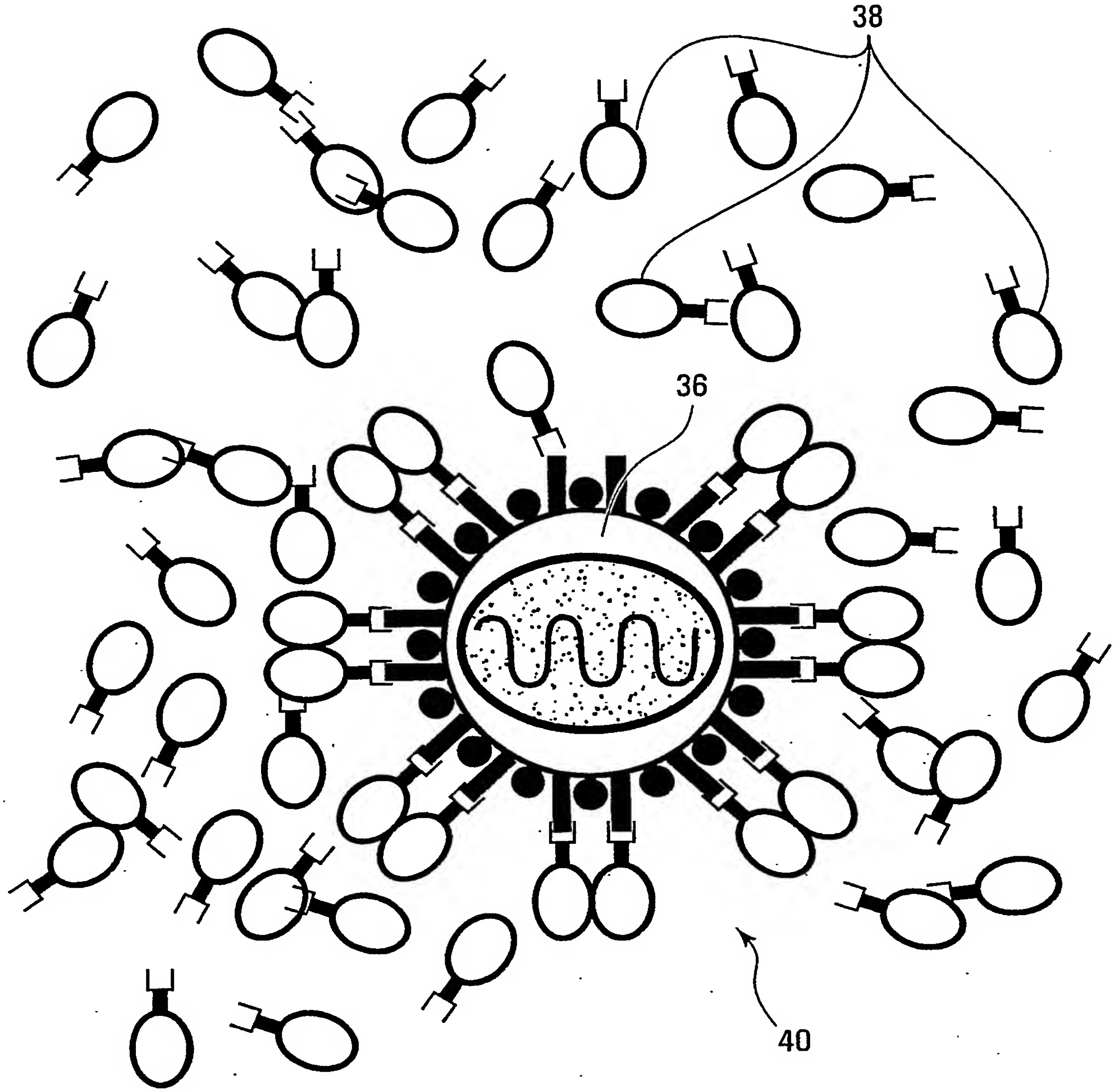
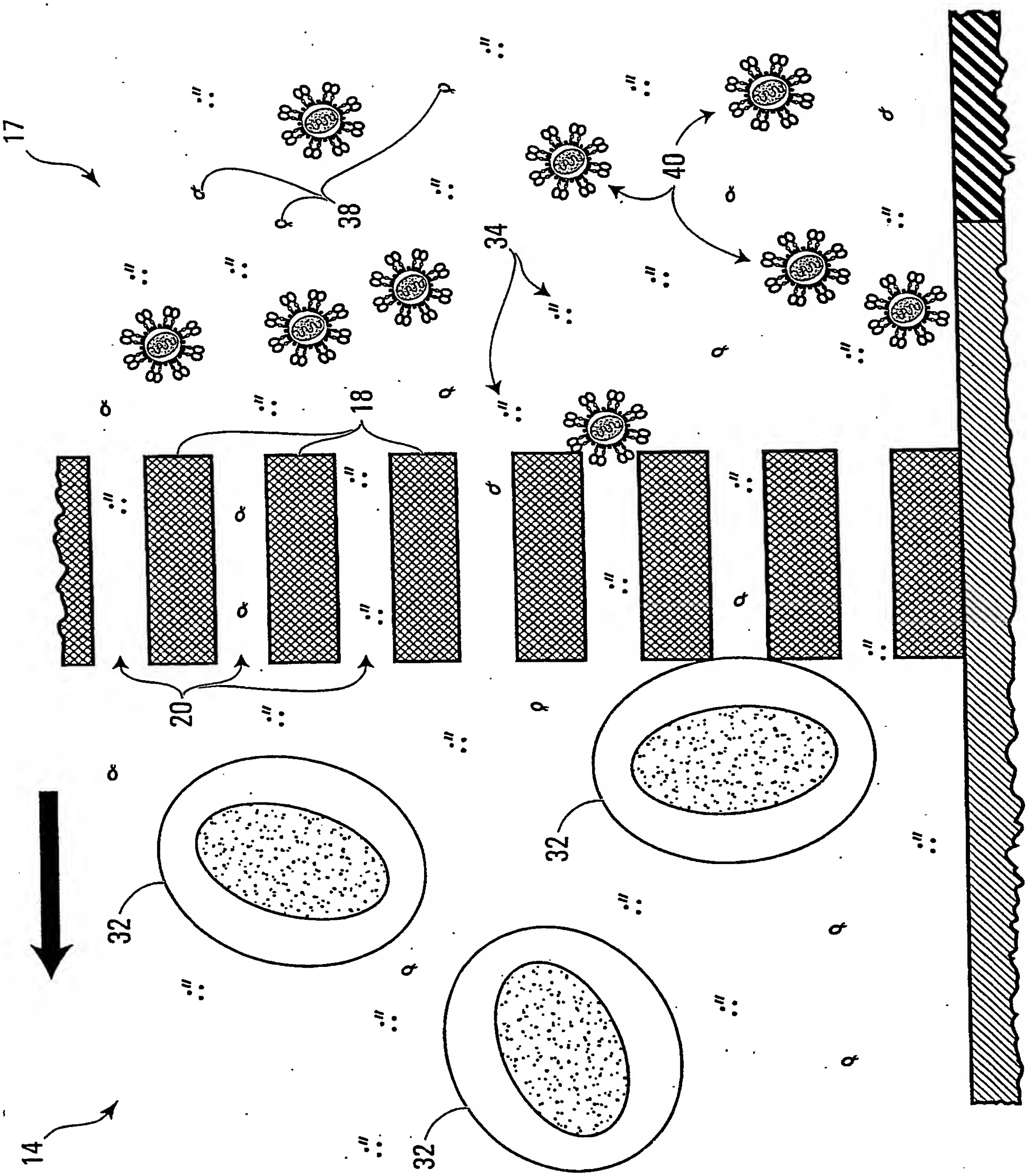


FIG. 3

FIG. 4



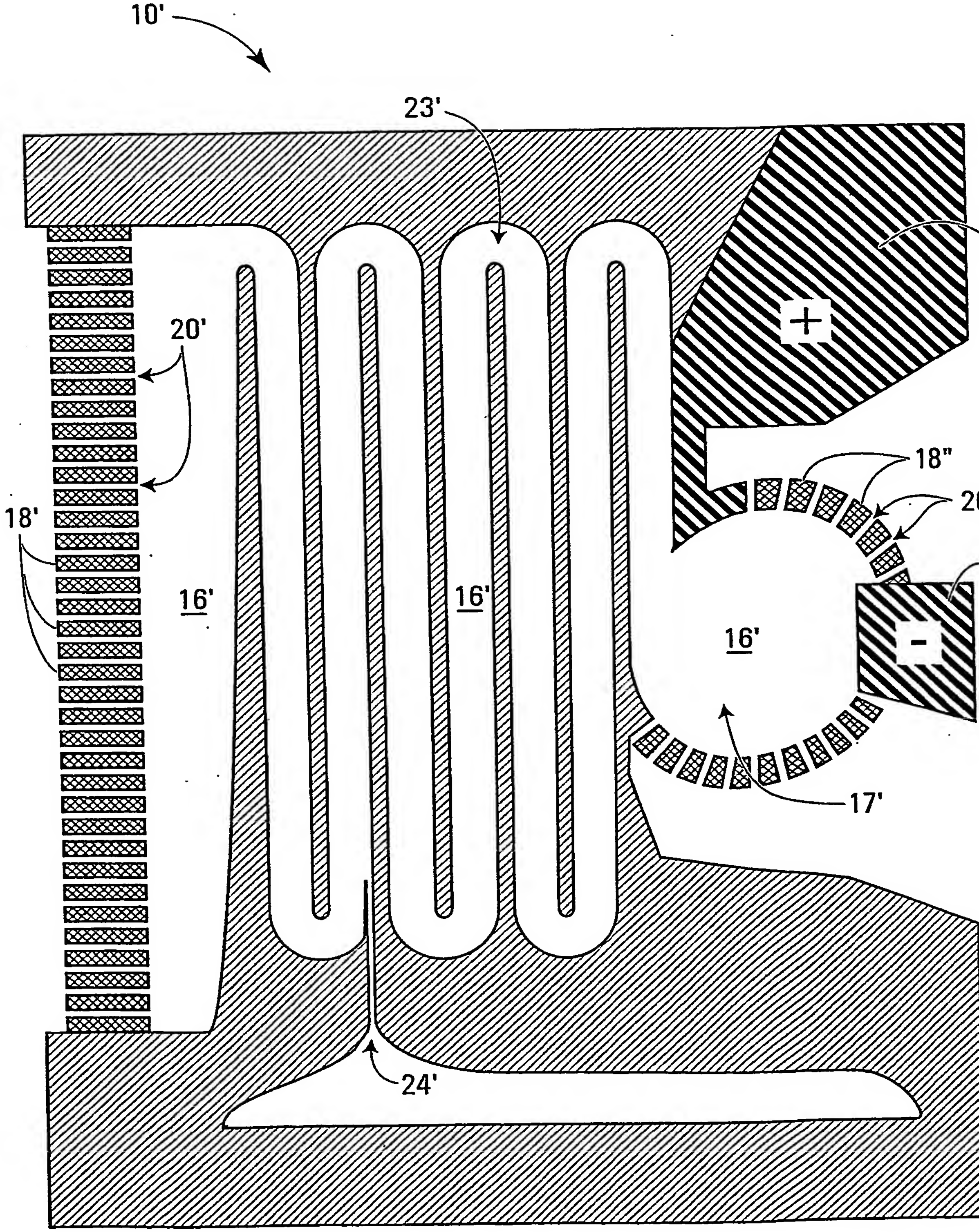


FIG. 5